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U.S. EPA HIGH PRODUCTION VOLUME CHEMICAL VOLUNTARY TESTING PROGRAM

CATEGORY JUSTIFICATION AND TEST PLAN

XYLENOL ISOMERS

Submitted by:
MERISOL USA LLC
Houston, Texas

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INTRODUCTION

Mixed Xylenols

Xylenols are liquids or crystals recovered from petroleum streams, coal coking operations and coal gasification. Several isomers are also produced synthetically. Xylenols are isomeric forms of dimethyl phenol containing two methyl groups attached to the ortho, meta, or para positions of the phenol ring. There are six possible isomeric forms of xylenol: 2,3-xylenol; 2,4-xylenol; 2,5-xylenol; 2,6-xylenol; 3,4-xylenol; and 3,5-xylenol. The boiling point range for these isomers is 201.1ºC to 227ºC.

Merisol's Process

Merisol's phenolic products are highly versatile materials that are used as intermediates in the manufacture of a wide variety of industrial products such as resins, flame retardants, antioxidants, and insulating varnishes. Merisol production of phenolics is essentially a recovery, purification, and fractionation operation. Merisol feedstocks are generally secondary streams from refineries, coal coking operations and coal gasification. From these feedstocks a multi-component phenolic mixture called "crude cresylic acid" is produced, which is composed of phenol, cresols, xylenols, ethylphenols, and, to a lesser extent, other higher boiling alkyl phenols. This mixture is processed to remove impurities, and then separated into various fractions by distillation. Distillation produces phenol, o-cresol, m- and p-cresol mixture, and fractions containing varying compositions of xylenols, ethylphenols, and higher boiling alkyl phenols. Merisol also has a proprietary process that produces p-cresol and m-cresol from the m-cresol and p-cresol mixture produced by distillation. Because of similarities in boiling points of components in the starting phenolic mixture, isolation of all pure xylenol isomers by distillation is not possible.[1]

Exposure Pattern for Mixed Xylenols

Merisol sells pure phenol, o-cresol, m-cresol and p-cresol. These are also sold in blends, as are the mixtures of xylenols and ethylphenols. The vast majority of xylenols and ethylphenols that Merisol produces and sells are contained in mixtures.[2] Therefore, public (and employee) exposure, as well as potential environmental exposures to Merisol's products, are primarily to blends and mixtures containing xylenols and/or ethylphenols. Because these Merisol products are generally moved into commerce as starting materials for further chemical processing, there is little consumer exposure to xylenols and ethylphenols. Merisol is by far the major, if not sole,

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[1] For the same reason, as discussed in Merisol's concurrently submitted proposal for ethylphenols, isolation of all pure m- and p-ethylphenols by distillation is not possible. Isolation of the o-ethylphenol isomer by distillation is possible, but has not proved to be commercially viable.

[2] Merisol is selling quantities of 3,4-xylenol that total 16,000 pounds, well below the HPV 1 million pound threshold. This 16,000 pounds is a portion of a 35,000 pound batch toll produced in Europe for Merisol more than three years ago as a developmental project.

U.S. producer of xylenols except for 2,6-xylenol (which is already the subject of a SIDS dossier).[3]

Merisol is a custom blender of phenolics. The number of different phenolic mixtures Merisol typically produces in a year is approximately 50, but can go as high as 100. These mixtures contain varying compositions of phenol, cresols, xylenols, ethylphenols, and higher boiling alkyl phenols. Xylenols, as well as ethylphenols, phenol, and cresols, are not components of every Merisol product mixture.

A breakdown of numbers of xylenol isomers contained in product mixtures is given in Text Table 1. Table 1 illustrates that Merisol products containing xylenol isomers (other than 2,6-xylenol which is already the subject of a SIDS dossier) include two to six different isomers in the products and that more than 60% of the xylenol products sold by Merisol have five or six xylenol isomers. The Merisol product containing all six xylenol isomers that is sold in the greatest volume and that contains the highest percentage of xylenol isomers is WES 297. This product contains 22.5% xylenols, the highest percentage in any Merisol product containing xylenol isomers.

Table 1: Distribution of Individual Xylenol Isomers
In Merisol Products

	Number of Different Xylenol Isomers Present as Components In Merisol Products					
	1 xylenol isomer in product*	2 xylenol isomers in product	3 xylenol isomers in product	4 xylenol isomers in product	5 xylenol isomers in product	6 xylenol isomers in product
% of total xylenol placed into commerce by Merisol	0.7	34.7	2.3	0.6	34.0	27.5

* 2,6-xylenol is the xylenol in the product (SIDS dossier available for this isomer).

[3] Merisol has imported 3,5-xylenol in quantities less than 1 million pounds per year for use in its mixtures and has imported 35,000 pounds of 3,4-xylenol (see footnote 2). Merisol understands that one other company may have imported 2,4-xylenol in quantities over 1 million pounds per year in 1999, 2000, and 2001 and that this quantity was used as an intermediate in the production of another substance. Less than 350,000 pounds of pure 2,5-xylenol have been imported into the U.S. in 2000 and 2001. Merisol understands that small amounts (<20,000 pounds per year) of pure 2,3-xylenol may have been imported into the U.S. in 2000 and 2001.

Exposure to xylenols, then, is primarily to a mixture of xylenol isomers. Accordingly, Merisol proposes that HPV data development for the Mixed Xylenols Category be completed on a mixture of the xylenol isomers.

DESCRIPTION OF THE CATEGORY

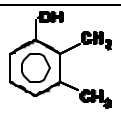
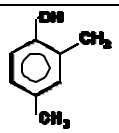
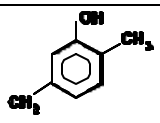
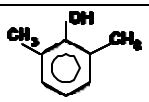
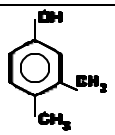
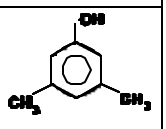
Mixed Xylenols

Each of the xylenol isomers (and an entity called "mixed xylenols") appears in the EPA HPV list of chemicals to be evaluated. Identification of the isomers is presented in Text Table 2, below. Although a CAS Registry Number has been assigned to "mixed xylenols," and mixed xylenols has been included as a test substance in the HPV Chemical Challenge Program, no definition of mixed xylenols (CAS# 1300716) is available, nor is there a single product or mixture understood by industry as "mixed xylenols." For purposes of the Mixed Xylenols Category, Merisol is defining mixed xylenols as a mixture containing portions of: xylenol isomers normalized to match the ratios of xylenol isomers occuring in the actual Merisol commercial product containing the highest percentage of all six xylenols, WES 297. The composition of the proposed Mixed Xylenol Test Mixture is:

Xylenol isomer	Mole % in Test Mixture
2,5-xylenol (CAS# 95874)	16.4
3,4-xylenol (CAS# 95658)	16.9
2,4-xylenol (CAS# 105679)	22.7
3,5-xylenol (CAS# 108689)	11.1
2,3-xylenol (CAS# 526750)	18.2
2,6-xylenol (CAS# 576261)	14.7.

This mixture mimics worker and consumer exposure to the highest percentabe of xylenols contained in an actual commercial product, but allows for the study of xylenol isomers without confounding effects of non-xylenol product components It is intended to represent the Category "Mixed Xylenols" for HPV data development, as well as each separate xylenol isomer. Each isomer is represented in the Category. Data developed on this Category are intended to represent all mixtures of xylenols, as well as the individual xylenol isomers.

Table 2: Xylenols – Chemical Name, CAS Number, and Structure

Chemical:	2,3-Xylenol	2,4-Xylenol	2,5-Xylenol	2,6-Xylenol	3,4-Xylenol	3,5-Xylenol
CAS Registry Number	526750	105679	95874	576261	95658	108689
Molecular structure						

CATEGORY JUSTIFICATION

Mixed Xylenols

As structural isomers, the members of the Mixed Xylenols Category share the same molecular weight, or in the case of the mixture, average molecular weight. The substituent groups on the phenolic ring are always methyl groups, so branching differences among the side groups is not a possibility in this Category. Examination of the physical-chemical properties for each isomer (Text Table 3) shows that the physical-chemical properties of the isomers are quite similar, due to the structural similarities. Of particular importance to environmental effects and potential human health effects are the values for octanol/water partition coefficient and water solubility. The values for octanol/water partition coefficient are 2.33 to 2.42 for each of the xylenols. Water solubility values at 25°C are reported to range from 3540 mg/L to 7870 mg/L. These values suggest that xylenol isomers and mixtures of isomers will distribute similarly in the environment and have similar residence times in environmental compartments. Bioaccumulation attributes will be similar among the isomers and the mixture also. Vapor pressures of the isomers at 25ºC range from 0.04 to 0.27 mmHg for the xylenols, also supporting a similar pattern of airborne distribution. Individually and as a group the xylenols are expected to exhibit low-to-moderate mobility in soil based on the $K_{o/w}$ values. Hydrolysis values have not been reported for xylenols, presumably due to the absence of a hydrolyzable functional group. Within the family of xylenol isomers, the physicochemical properties are expected to manifest similar effects on the environment and potentially on human health.

The biological response patterns of xylenols, like the physicochemical properties, derive from the structural similarities of the isomers. There are data from independent sources to support this position by way of example or illustration. For instance, in work completed by the National Toxicology Program (NTP) with a group of structurally-related isomers, in this case methyl phenols, or cresols, toxicology studies showed that there was no one predominantly toxic isomer and that target organs for toxicity and toxic effect dose levels were relatively consistent across the isomers. This is expected to be the case for xylenols.

Table 3: Xylenols Physical Properties

Chemical	2,3-Xylenol	2,4-Xylenol	2,5-Xylenol	2,6-Xylenol	3,4-Xylenol	3,5-Xylenol
CAS Registry Number	526750	105679	95874	576261	95658	108689
Boiling Point	216.9ºC	211.0ºC	211.2ºC	201.1ºC	227.0ºC	221.7ºC
Melting Point	72.6ºC	24.5ºC	74.8ºC	45.6ºC	62.1ºC	63.4ºC
Octanol/Water Partition Coefficient	2.42	2.36	2.36	2.36	2.33	2.35
Water Solubility	4750 mg/L @ 25ºC	7870 mg/L @ 25ºC	3540 mg/L @ 25ºC	6050 mg/L @ 25ºC	4760 mg/L @ 25ºC	4880 mg/L @ 25ºC
Vapor Pressure	0.09mmHg@ 25ºC	0.11mmHg@ 25ºC	0.16mmHg@ 25ºC	0.27mmHg@ 25ºC	0.04mmHg@ 25ºC	0.04mmHg@ 25ºC
Biodegradation	Complete in unac-climated soil 19 days	Unac-climated soil $T_{1/2}$ = 3.5days	Complete in activated sludge 5 days	Complete in ac-climated soil 5-14 days	Complete in unac-climated soil 9 days	Complete in unac-climated soil 11 days
Photodegradation in Air	$T_{1/2}$ = 4.8 hrs	$T_{1/2}$ = 5.3 hrs	$T_{1/2}$ = 4.8 hrs	$T_{1/2}$ = 5.8 hrs	$T_{1/2}$ = 4.7 hrs	$T_{1/2}$ = 3.4 hrs

NA = Not Available

Toxicology and Environmental Fate of Xylenol Isomers

a. Mammalian Acute and Repeated Dose Toxicity

Mammalian toxicity testing of 2,6-xylenol, the most thoroughly tested isomer, is limited. The acute oral LD50 is most reliably reported as 1470 mg/kg. Values of 296-1750 mg/kg are reported for rats and other species. (SIDS, 1997). Acute dermal penetration (LD50) studies have been completed in rats, mice and rabbits and the resulting LD50 values range from 920 to over 2325 mg/kg (SIDS, 1997). The acute inhalation LC50 in rats is reported to be >270 mg/m^3 for a 4-hour exposure, and 2,6-xylenol is reported to be a strong skin and eye irritant (SIDS, 1997). It was negative in a Guinea pig study for dermal sensitization (SIDS, 1997).

Rodent oral LD50 values for other xylenol isomers from unpublished reports (or secondary source reports) are: 444 mg/kg, 400 mg/kg, 2300 mg/kg, 608 mg/kg and 56 mg/kg for 2,5-, 3,4-, 2,4-,3,5- and 2,3-xylenol, respectively. The lack of detail presented in the study reports and possible overall quality of these reports should be considered when comparisons are made about comparability of acute toxicities across isomers.

Repeated-dose toxicity has been studied for 2,6-xylenol. In oral gavage studies ranging from 28 days to 10 months with rats and in one case, mice, 2,6-xylenol produced damage to the liver and glandular stomach(28-day study) and to the liver, spleen, heart and kidney (10 month study). Rats tolerated 100 mg/kg/day for shorter-term exposures (28 days). According to a translation of the Russion work, the LOAEL for a 10-month study was 6 mg/kg/day and the NOAEL was reported to be 0.06 mg/kg/day (SIDS, 1997). Although of shorter duration, the 28-day study is presented in Table 4 instead of the 10-month study because of the greater reliabity that can be assigned to the study report. Support for the Category comes from the most reliable studies of repeated-dose toxicity across the isomers, the 90-day study on 2,4-xylenol and the 28-day study on 2,6-xylenol. These provide NOAEL values that are quite similar: 50mg/kg/day in the 90-day study and something between 20-100 mg/kg/day in the 28-day study. The authors of the 28-day study reported separate NOAEL values by test animal sex. A simple average, although not strictly justified, would be 60 mg/kg/day, which compares well to the 90-day NOAEL for 2,4-xylenol.

b. Reproductive and Developmental Toxicity

There are no reports of reproductive toxicity studies conducted with any xylenol. An oral gavage developmental toxicity study in rats has recently been completed with the 2,6 isomer. The NOAEL for developmental toxicity was 180 mg/kg/day, based on reduction in fetal weight. The NOAEL for maternal toxicity was 60 mg/kg/day based on body weight gain suppression and decreased food consumption (SIDS, 1997).

c. Genetic Toxicity

Each of the xylenol isomers, except 3,5-xylenol, has been evaluated in bacterial mutation tests usually with two (TA98 and TA 100) Salmonella strains. 2,6-Xylenol was tested with four strains. The work was completed with and without exogenous metabolic activation, and was negative for gene mutation. Most of this work is published.

2,6-Xylenol is reported to be negative for gene mutation in bacterial and mammalian cell assays, with and without exogenous metabolic activation (SIDS, 1997). *In vitro* cytogenetics testing with V79 cells produced signs of chromosomal aberration; *in vivo* testing (rat bone marrow, oral gavage) was negative for chromosome effects, including aberration (SIDS, 1997).

d. Environmental Toxicity and Environmental Fate

The acute aquatic environmental toxicity of the xylenols has been characterized in several marine and freshwater fish and invertebrate species using static and flowthrough exposure procedures. The EC50 values issuing from these studies range from 3 to 53 mg/L for fish and 2.1 to 16.5 mg/L for daphnia. These values are from unpublished studies or secondary sources. An algal test and a biodegradation evaluation have been completed on 2,6-xylenol.

Biodegradaton of each of the xylenol isomers has been investigated and reported. Aerobic and anaerobic degradation studies from several environmental media (activated and unactivated soils, sludge and sediments) indicate that complete degradation of each isomer

occurs in less than 21 days (the half-life for 2,4-xylenol in unacclimated soil was 3.5 days). Accordingly, xylenols are readily biodegraded in the environment.

There is potential for the direct photolysis of each of the xylenol isomers, since an absorption band extends over 290 nm and the xylenols may absorb light in the environmental UV spectrum. The manufacture and use pattern for xylenols does not afford significant opportunity for UV light exposure, so the importance of this mechanism for degradation would be limited to spills of the xylenols or xylenol-containing products. In air, xyenols are relatively photolytic with photolysis half-lives of less than 6 hours.

Table 4: Xylenols Category Data

	Acute mam-malian toxicity	Repeat dose toxicity	Gene tox (point mutat)	Gene tox (chrom-osome)	Repro-tox	Devel-opment tox	Acute fish tox	Acute daphnia tox	Algal tox	Biodeg
2,5-xylenol	Rat oral 444 mg/kg	ND	Neg Ames	ND	ND	ND	EC50= 3-5 mg/L	EC50 10 mg/L	ND	Readily biode-gradable See Table 3
3,4-xylenol	Mouse oral 400 mg/kg	ND	Neg Ames	ND	ND	ND	EC50= 15mg/L	ND	ND	Readily biode-gradable See Table 3
2,4-xylenol	Rat oral 2300 mg/kg	3 Mo oral mouse NOAEL 50 mg/ kg/day	Neg Ames	ND	ND	ND	EC50= 17mg/L	EC50= 2.1mg/l	ND	Readily biode-gradable See Table 3
3,5-xylenol	Rat oral 608 mg/kg	ND	ND	ND	ND	ND	EC50= 53mg/L	ND	ND	Readily biode-gradable See Table 3
2,3-xylenol	Rat oral LD50 56mg/ kg	ND	Neg Ames	ND	ND	ND	ND	EC50= 16mg/L	ND	Readily biode-gradable See Table 3
2,6-xylenol	Rat oral 1470 mg/kg	28 day rat oral NOAEL 20mg/kg/ day for female 100mg/k g/day for males	Neg Ames	Neg *In vivo Rat* NOAEL >1400 mg/kg/ day	ND	Rat Maternal NOAEL 60mg/kg Devel NOAEL 180mg/ kg	EC50= 27mg/L	EC50= 11mg/L	LC100 325 mg/L	Readily biode-gradable See Table 3

ND = No Data

Xylenols are dimethyl phenols, and there is experience with methyl phenols that can illustrate and support the Mixed Xylenols Category propsed by Merisol for HPV data generation. The toxicological justification for the Mixed Xylenols Category is that existing studies of structurally related compounds, methyl phenols (also known as cresols), have demonstrated that the methyl phenol isomers are remarkably equivalent in toxicity and that binary and tertiary mixtures of cresol isomers do not produce toxic interactions among the isomers, *i.e.*, that mixtures of cresol isomers do not exhibit more than additive toxicity.[4] We describe the cresol data below because we believe that the xylenol isomers will act analogously based on their similar chemical/physical properties; we do not believe, however, that the data support otherwise relying on the cresols data for conclusions about mixed xylenols with regard to HPV testing requirements, and we do not present these data for that purpose.

Attachment 1 to this document presents in tabular form summaries of developmental and reproductive toxicity data, as well as genetic toxicity data on methyl phenol isomers. From inspection of the Attachment 1 tables, it can be seen that within a test animal species (rabbit or rat), methyl phenol (cresol) isomers exhibited similar or the same toxicity. Effective doses, expressed as NOAELs, remained constant or very close across isomers, never more than one dose level apart. Target organs for isomer toxicity and systemic toxic effects were nearly superimposable across isomers. This qualitative and quantitative comparability of toxicity across isomers exhibited in the cresols data set is consistent with cresol isomers results described by Dennis Deitz, cited in the footnote above. Genetic toxicity studies of the cresol isomers show few inconsistencies in test results across isomers. In the seven cases where there are data on a

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[4] In 28-day feeding studies conducted on cresol isomers by the NTP, mice and rats were treated with equivalent dose levels of each isomer and in 90-day studies rats received equivalent doses of ortho-cresol or the meta/para-mix. The author of the study, Dennis Dietz, observed so little difference among the cresol isomers in toxicity (both concentration and dose effects) that he chose to summarize the results of the 28- and 90-day studies together. In summarizing the subchronic toxicity of cresol isomers, Dietz said:

> The cresol isomers exhibited a generally similar pattern of toxicities in rats and mice. Dietary concentrations of 3,000 ppm appeared to be minimal effect levels for increases in liver and kidney weights and 15,000 ppm for deficits in liver function. Histopathologic changes, including bone marrow hypocellularity, irritation to the gastrointestinal tract and nasal epithelia, and atrophy of female reproductive organs, occasionally occurred at 10,000 ppm, but were more common at the high dose of 30,000 ppm (Ref. NTP, 1992).

In these studies, which included an assessment of individual isomers and an isomer mix, no evidence of toxic interaction was reported by the author, Dietz. In the final report of those studies, Dietz concluded that "In summary, the various cresol isomers exhibited a generally similar spectrum of toxicities in these studies, with few exceptions as noted previously. There was little evidence to suggest a significant increase in toxicity with longer exposures in the 13-week study when compared to the effects seen with similar doses in the 28-day study."

mixture of the isomers, as well as data on one or more isomers, there is no difference in results in those cases (two) where data are available on each isomer and the mixture. In another case, the positive assay result for the mixture can be attributed to a positive result for an isomer in the same test. In the remaining four examples, isomeric uniformity of genetic activity cannot be affirmed or refuted because of the incomplete data set.

The toxicological equivalence or near equivalence of methyl phenols (cresols) derives from the structural similarity shared by members of the group (isomeric forms of methyl phenol) and the similarity in chemical/physical properties which follows from the structural relationship. In an analogous manner, a complementary structure-activity relationship is anticipated with dimethyl phenols (xylenol isomers) based on the structural similarity among this group of isomers. The demonstration of a structure-activity relationship among the methyl phenol isomers and the expectation of a parallel structure-activity relationship for the homolog dimethyl phenols is the toxicological justification of the Mixed Xylenols Category for HPV testing.

CATEGORY TEST PLAN

From inspection of Table 4, it can be seen that where complementary data exist on isomers, a concordance in results is apparent. Merisol notes that only a portion of the testing on 2,6-xylenol (some in mammalian cell *in vitro* mutation work, *in vivo* cytogenetics, and the developmental toxicity study) was conducted and reported under GLP conditions. Many details for the remainder of the work on xylenols are unavailable. Thus, while the existing mammalian and ecological toxicology data, when viewed as a whole, strongly support toxicology data development on a xylenol mixture as a category for HPV testing, the data may not in every case be adequately reported to be relied upon for HPV evaluations.

Merisol proposes that submitted data for physiochemical properties, photodegradation, biodegradation, and toxicity to fish and invertebrates are sufficient for addressing these endpoints for the HPV Challenge Program. Merisol also proposes not to perform hydrolysis testing, which is not appropriate for these substances, and determination of fugacity endpoint, which is fulfilled by modeling and cannot be run appropriately with mixtures. Accordingly, Merisol proposes that the studies listed in Table 5 will be developed on the Mixed Xylenol Test Mixture (composition shown below) and data from those studies used to supply data for SIDS endpoints in the Mixed Xylenols Category.

Xylenol isomer	Mole % in Test Mixture
2,5-xylenol (CAS# 95874)	16.4
3,4-xylenol (CAS# 95658)	16.9
2,4-xylenol (CAS# 105679)	22.7
3,5-xylenol (CAS# 108689)	11.1
2,3-xylenol (CAS# 526750)	18.2
2,6-xylenol (CAS# 576261)	14.7.

This mixture is intended to represent the Category “Mixed Xylenols” for HPV data development, as well as each separate xylenol isomer.

Data developed on this Category are intended to satisfy all requirements under the HPV Challenge Program for all mixtures of xylenols, as well as the individual xylenol isomers.

CONCLUSION

Xylenol mixtures sold or distributed in the U.S. by Merisol are of variable composition. Testing every possible variation would violate animal use goals without producing additional meaningful scientific information, and would thus also be unnecessarily burdensome. Because exposure of people and the environment is primarily to mixtures of xylenols, data developed on a mixture of six xylenols will provide cogent and reliable information for assessment of the potential hazards its xylenol-containing products may present to humans and the environment. This approach to data development also will account for any interactions between xylenol isomers that may impact toxicity, although none are expected.

Merisol proposes a category approach for testing mixed xylenols. The testing is to account for each of the xylenol listings on EPA's HPV list of chemicals to be tested.

Table 5: Mixed Xylenols Category HPV Test Plan

HPV DATA ENDPOINT	PROPOSED DATA DEVELOPMENT METHOD
1. HEALTH EFFECTS	
Acute Toxicity	Acute Oral Toxicity: OECD Health Effects Test Guideline 425
Repeat Dose Toxicity	Combined Repeat-Dose Toxicity Study with Reproductive/ Developmental Toxicity Screen: OECD Health Effects Test Guideline 422
Repro-Develop. Toxicity	
Genetic Toxicity	Bacterial Mutation Test: OECD Health Effects Test Guideline 471; *In vitro* chromosomal aberration test OECD Guideline 473
2. ECOTOXICITY	
Algae	Acute Toxicity to Aquatic Plants (Algae): OECD Test Guideline 201

REFERENCES

NTP Report on the Toxicity Studies of Cresols in F344/N Rats and B6C3F1 Mice. Dennis Dietz, US Department of Health and Humans Services, February, 1992.

Reduced SIDS Dossier: 2,6-Dimethylphenol, CAS Number 576-26-2, Sponsor Country USA, September 2, 1997.

ATTACHMENT 1

Mammalian reproductive/developmental toxicity summaries and genetic toxicity summaries of methyl phenol isomers (o-, m-, and p-cresol)

CRESOLS ISOMER MAMMALIAN TOXICITY COMPARISON

STUDY NOAEL	o-CRESOL	m-CRESOL	p-CRESOL
Rabbit Oral Gavage Developmental Toxicity: Maternal NOAEL & Effect/Target Organ	NOAEL = 5 mg/kg/day Maternal LOAEL = 50 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes.	NOAEL = 5 mg/kg/day Maternal LOAEL = 50 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes.	Maternal NOAEL = 5 mg/kg/day Maternal LOAEL = 50 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes; 15% and 35% mortality in mid- and high-dose vs. 0% in controls.
Rabbit Oral Gavage Developmental Toxicity: Developmental NOAEL & Effect/Target Organ	Developmental NOAEL = 50 mg/kg/day No embryotoxicity or fetotoxicity. Skeletal variations observed in high-dose pups (100 mg/kg/day)	Developmental NOAEL= 100 mg/kg/day No embryotoxicity or fetotoxicity.	Developmental NOAEL = 100 mg/kg/day No embryotoxicity or fetotoxicity.
Rat Oral Gavage Developmental Toxicity: Maternal NOAEL & Effect/Target Organ	Maternal NOAEL 175 mg/kg/day Maternal LOAEL = 450 mg/kg/dayHypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 16% mortality.	Maternal NOAEL = 175 mg/kg/day Maternal LOAEL = 450 mg/kg/day Hypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 0% mortality.	Maternal NOAEL =175 mg/kg/day Maternal LOAEL = 450mg/kg/day. Hypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 12% mortality.
Rat Oral Gavage Developmental Toxicity: Developmental NOAEL & Effect/Target Organ	Developmental NOAEL = 175 mg/kg/day No increase in malformations, visceral variations at the high-dose.	Developmental NOAEL= 450 mg/kg/day No increase in malformations. No increase in variations.	Developmental NOAEL = 175 mg/kg/day No increase in malformations, skeletal variations at the high-dose.
Two-Generation Reproductive Toxicity in Rats by Oral Gavage: Parental NOAEL & Effect/Target Organ	Parental NOEAL 30 mg/kg/day Parental LOAEL = 175 mg/kg/day. Transient hypoactivity, audible respiration, ataxia, twitches, tremors, initially decreased food consumption and body weight gain, 52%-28% mortality across sexes and generations. No lesions specifically noted in organs from F0 and F1 adult necropsy.	Parental NOAEL <30 mg/kg/day Effects included high-dose mortality (450 mg/kg/day). Transient hypoactivity, audible respiration, ataxia, twitches, tremors, initially decreased food consumption and body weight gain, 40%-12% mortality across sexes and generations. Brain hemorrhage, atrophied seminal vesicle, lung congestion noted at necropsy of F0 and F1 parents.	Parental NOAEL = 30 mg/kg/day Parental LOAEL = 175 mg/kg/day. High-dose mortality (450 mg/kg/day). Transient hypoactivity, audible respiration, ataxia, twitches, tremors, initially decreased food consumption and body weight gain, 40%-4% mortality across sexes and generations. Lung congestion noted at necropsy of F0 parents, atrophied seminal vesicle and lung congestion noted at necropsy of F1 parents.
Two-Generation Reproductive Toxicity in Rats by Oral Gavage: Offspring NOAEL & Effect/Target Organ	F1 and F2 NOAEL = 175 mg/kg/day No gross lesions in F1 or F2 pups.	F1 and F2 NOAEL = 175 mg/kg/day No gross lesions in F1 or F2 pups.	F1 and F2 NOAEL = 175 mg/kg/day No gross lesions in F1 or F2 pups.

SUMMARY OF CRESOLS MUTAGENICITY DATA

ASSAY	TEST SUBSTANCE			
GENE MUTATION	ORTHO	META	PARA	MIXED
SALMONELLA ACTIVATION	-	-	-	-
SALMONELLA NONACTIVATION	-	-	-	-
MOUSE LYMPHOMA ACTIVATION	-	nd	nd	+
MOUSE LYMPHOMA NONACTIVATION	-	nd	nd	nd
*MOUSE LYMPHOMA ACTIVATION	Nd	-	-	nd
*MOUSE LYMPHOMA NONACTIVATION	Nd	-	-	nd
*SLRL DROSOPHILA	-	nd	-	nd
DNA EFFECTS				
UDS	-	nd	+	+
*HEPATOCYTE UDS	Nd	-	nd	nd
CHROMOSOME DAMAGE				
ROOT TIP	+	+	+	nd
SCE ACTIVATION	?	-	-	+
SCE NONACTIVATION	?	-	-	+
*CHO CYTOGENETICS ACTIVATION	+	-	+	nd
*CHO CYTOGENETICS NONACTIVATION	+	-	+	nd
*MOUSE (IN VIVO) CYTOGENETICS	Nd	-	nd	nd
*MOUSE DOMINANT LETHAL	-	nd	-	nd
MOUSE MICRONUCLEUS				-
CELL TRANSFORMATION				
BALB/C 3T3 ACTIVATION	-	nd	nd	+
*BALB/C 3T3 ACTIVATION	-	-	nd	nd
*BALB/C 3T3 NONACTIVATION	Nd	-	+	nd
C3H10T1/2 ACTIVATION	Nd	nd	+	nd
C3H10T1/2 NONACTIVATION	Nd	nd	nd	nd

* ACC PANEL ASSAYS

nd = No Test Data
+ = Positive for Genetic Toxicity
- = Negative for Genetic Toxicity
? = Equivocal Results for Genetic Toxicity

REFERENCES: ATTACHMENT 1

Developmental Toxicity and Reproductive Toxicity References:

R. W. Tyl, Unpublished Report Number 51-508: "Developmental Toxicity Evaluation of o-, m-, or p-cresol Administered by Gavage to New Zealand White Rabbits," Bushy Run Research Center, Export, Pa., June 27, 1988.

R. W. Tyl, Unpublished Report Number 51-509: "Developmental Toxicity Evaluation of o-, m-, or p-cresol Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., June 29, 1988.

T. L. Neeper-Bradley and R. W. Tyl, R. W. Tyl, Unpublished Report Number 51-634: "Two Generation Reproduction Study of m-Cresol, Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., February 28, 1989.

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T. L. Neeper-Bradley and R. W. Tyl, R. W. Tyl, Unpublished Report Number 51-512: "Two Generation Reproduction Study of p-Cresol, Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., March 28, 1989.

Genetic Toxicity References:

IUCLID Data Sheet: o-Cresol CAS Number 95-48-7, European Chemicals Bureau, February 11, 2000.

IUCLID Data Sheet: m-Cresol CAS Number 103-39-4, European Chemicals Bureau, June 19, 1997.

IUCLID Data Sheet: Mixed Cresols CAS Number 1319-77-3, European Chemicals Bureau, March 1, 2001.